

625 in 1956, 653 in 1957, 688 in 1958, 733 in 1959, and 873 in 1960 (case-records all personally scrutinized). Allowing for a 2.8% annual increase in population, the yearly admissions per 100,000 population were 71, 81, 82, 84, 87, and 102. Since there was a disproportionate rise in admissions to Sungei Patani Hospital (136 in 1955 and 341 in 1960), we think greater use of hospitals is a more important factor than a progressive increase in snake-bite incidence in explaining these figures. Yet observers say there are more *A. rhodostoma* snakes than in pre-war days. This increase is ascribed to more undergrowth on the rubber estates, where less weeding has been carried out in the post-war era partly for economic reasons but also because the undergrowth prevents land erosion.

The variables in age, sex, race, location, time and circumstances of bite, and site of the bite all reflect the rural and occupational nature of the snake-bite hazard. It is noteworthy that only 18 of the 1,032 Central Kedah bites occurred in the main town. The very high incidence of bites among rubber-estate weeders is another striking feature. In Malaya the pit viper *A. rhodostoma* is much the most common species biting human victims. Because it is confined to the north in Malaya, over two-thirds of all snake-bite cases in the country take place in this region. *A. rhodostoma* is a more common cause of severe poisoning than sea-snakes or cobras. Bites from the two pit vipers *Trimeresurus wagleri* (Boie) and *T. purpureomaculatus* (Gray) rarely result in serious poisoning, and no fatality has so far been ascribed to them. Bites from the other four viper species occurring in Malaya, from king cobras, kraits, and coral snakes are extremely rare.

In our opinion the most practical single means of reducing the snake-bite hazard in Malaya would be wearing shoes or preferably boots. Long trousers would give added protection, although they are not popular among rural folk. Precautionary advice such as "Watch where you put your hands and feet" (Klauber, 1956) is unlikely to make any serious impact in rural districts of Malaya, where the markings of *A. rhodostoma* form ideal camouflage against the background of weeds and rubber leaves. Thus one of our patients saw a nest of snake eggs (*A. rhodostoma*), carefully looked around, and after satisfying himself there was no snake in the vicinity picked up the eggs. He was promptly bitten by the mother, who was lying among leaves by the side of the eggs. Reduction of poisonous snakes by killing or trapping campaigns, bounties, and so on are unlikely to succeed (when rewards were made available in India, enterprising individuals started to breed snakes specially for the bounties).

In countries where snake bite is a serious medical problem there has been little controversy over first-aid measures. The rural people have time-honoured methods which are sensible and—much more important—harmless. They virtually never use meddlesome local measures such as incision, and therefore bacterial infection is correspondingly rare, occurring only as a late complication of necrosis.

The low morbidity and mortality in human snake bite is remarkable (see Table VI). In many cases we have obtained enough venom to kill several adult human beings by milking snakes shortly after they had bitten patients. This confirms a previously stated belief (Reid, 1957) that snake bite in humans is a defensive reaction which rarely results in much venom being injected. In the light of these figures it is easy to understand how

success may be (and has been) claimed for virtually any treatment in snake bite. The data also emphasize that young victims are no more susceptible to poisoning than older ones. The clinician must judge each patient individually. Thus, excluding 199 subjects in therapeutic trials, only 376 (39%) out of the remaining 960 patients required antivenene.

### Summary

A prospective epidemiological study of 1,159 patients bitten during a three-year period in north-west Malaya confirms that snake bite is a rural and occupational hazard.

The pit viper *Ancistrodon rhodostoma* (Boie) causes 85% of the bites in north-west Malaya, where snake bite is a serious medical problem.

In 824 of the 1,159 cases the snake was reliably identified as a potentially lethal viper, cobra, or sea-snake. Yet 53% of these 824 victims escaped with slight or no poisoning. Poisonous snake bite is *not* synonymous with snake-bite poisoning.

We wish to thank Mr. Baharom, hospital assistant at Sungei Patani Hospital, for his unstinted help in observation and care of patients and for much other work connected with this study.

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## BRUNETTE TO BLONDE

### DEPIGMENTATION OF HUMAN HAIR DURING ORAL TREATMENT WITH MEPHENESIN

BY

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The hazards of modern medical treatment are now so real and diverse that it is wise to inquire routinely not only about the patient's symptoms but also about previous treatment—including that prescribed by oneself. The pills in the handbag may disclose the cause of complaints which extensive hospital investigation might fail to explain. Recent personal experiences include cycloserine epilepsy, chloroquine ("nivaquine") retinopathy, and methyldopa ("aldomet") fever. Fortunately the side-effects of many drugs are unpleasant and appear early. Some of course are insidious and late. But what if they are not only insidious but also not unpleasant? What if the effect is actually pleasing to the patient? The following experience suggests that the patient may not then mention it to the doctor and the particular side-effect may not come to light for some time.

### Case 1

A housewife aged 37 was first seen in December, 1958, and was found to be suffering from multiple sclerosis. Mephenesin carbamate ("tolseram") 0.5 g. t.d.s. was prescribed for muscular spasms, and in due course the dose was increased to 2 g. five times daily. I saw her next in May, 1959, when there was nothing unusual to report—or so I thought. I did not see her again until October, 1961, when she "looked"

different, and I mentioned this to her husband at the end of the consultation. They looked at each other, smiled knowingly, and hinted that my suspicion might have some foundation. I was encouraged to try to identify the change



FIG. 1.—Case 1. Blonde hair during mephenesin treatment.



FIG. 2.—Case 1. Dark hair three months after mephenesin was withdrawn.

Her hair was photographed (Fig. 1), the mephenesin was stopped, and her hair returned to its original dark-brown colour in three months (Fig. 2).

### Case 2

This patient was a spinster of 46, with a right spastic hemiplegia following a head injury in infancy. Her main disability consisted of gross spasmodic muscular contractions of the affected arm. She had had these for many years, and when I placed her on mephenesin in May, 1957, the effect was most gratifying. With gradually increasing doses these movements practically ceased. For three years, from 1957 to 1960, she took between 10 and 12 g. of the drug daily and reported no ill effects. During 1960 she found that the drug was gradually losing its effect, and in June I replaced it by biperiden ("akineton") and subsequently tigloidine ("tiglyssin").

In October, 1961, I learned that her hair turned from brunette to blonde during the first three months of treatment

with mephenesin in 1957. It returned to its normal colour in about the same period of time in the summer of 1960, when the drug was stopped. No change in her skin was noticed. As in Case 1, none of her friends or relatives had been let into the secret. A further course of mephenesin confirmed her statements.

After a few mistakes I suggested that she had bleached her hair. She was then a blonde. I was assured that in fact her hair had lost its brunette shade during the first four months of treatment with mephenesin. She had never bleached her hair, but she had not denied it when her friends and relatives (excluding her husband, who approved the change) had made the suggestion. They had informed no one, including myself when I had seen her in May, 1959, at a time when her hair had already lightened considerably. They both liked the change, and I must confess the tint of the hair—a light golden—was very pleasing to the eye. There was some lightening of her body hair but it was much less obvious. There was no noticeable depigmentation of her skin, and her few freckles had persisted unchanged. The colour of the iris (brown) had not altered.

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During the past year all patients (approximately 40) on mephenesin have been asked about their hair, and four further examples of this drug effect have been observed (two males and two females). No depigmentation of skin was present. All were suffering from multiple sclerosis. In the two males depigmentation was slight, and as they were both greying it is not possible to be certain about the effect of the drug. In the two females the effect was pronounced in one (Case 3) and moderate in the second (Case 4). No other side-effects were noted, and lightening of hair colour seems to occur only in patients who can tolerate the upper range of doses of the drug recommended by the manufacturers (1 to 3 g. three to five times daily) for several months.

### Case 3

A housewife aged 33 was prescribed mephenesin in November, 1959. When she had taken 20 tablets (10 g.) a day for about three months she noticed that her hair was turning blonde, but although she was attending the neurological clinic regularly she did not mention it until specific inquiry was made by Dr. Brian Lentle in April, 1962. She was then a definite blonde (Fig. 3). Within two weeks of stopping the drug the roots of her hair became dark. She was so distressed by the return of muscular spasms that



FIG. 3.—Case 3. Blonde hair during mephenesin treatment.



FIG. 4.—Case 3. Middle zone of dark hair representing six weeks' growth when patient was not taking mephenesin. Note blonde roots and ends of hairs which grew when she was taking mephenesin.

mephenesin was restarted after six weeks. By July, 1962, her hair was blonde at the roots, dark in the middle,



FIG. 5.—Case 3. Dark hair, ten weeks after mephenesin was withdrawn

and blonde at the ends (Fig. 4). The middle zone of dark hair represented the growth which took place when mephenesin was withdrawn. Pubic and axillary hair was only slightly affected. In October, 1962, after a further period of ten weeks without the drug, her hair had reverted to its normal brunette shade (Fig. 5).

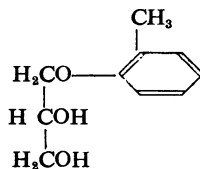
#### Case 4

This patient, a spinster aged 34, has found that she

cannot tolerate more than 5 g. of mephenesin daily because of giddiness and nausea. Nevertheless she has noticed that her hair lightens considerably, and photographic records confirm her observation.

#### Discussion

Although there is no published report to the effect, there can be no doubt that mephenesin carbamate can cause depigmentation of human hair. Mephenesin is an aromatic glycerol ether— $\alpha$ : $\beta$ -dihydroxy- $\gamma$ -(2-methylphenoxy) propane.



Experimental studies have shown that it exerts a depressant effect on synaptic transmission at spinal, brain-stem, and subcortical levels. Neuronal conduction and neuromuscular transmission are unimpaired. It also possesses local anaesthetic and anticonvulsant properties. It has no known biochemical effect on melanogenesis.

Mammalian hair colour seems to depend on two types of pigment (Lerner and Case, 1959): a dark-brown or black pigment (eumelanin), derived from tyrosine, and a yellow or red pigment (phaeomelanin) of unknown origin. There is some suggestion that the latter may be derived from tryptophan. Melanin is a protein conjugate formed enzymically by the reaction of tyrosinase, a copper-containing enzyme belonging to the class of phenolases, with oxygen and tyrosine. Melanin is formed in highly specialized secretory cells—the melanocytes derived from the neural crests and located in the skin, eyes, and nervous system. Melanocytes are located in the epidermal-dermal junction and in the hair bulb, and are able to transfer granules of melanin into neighbouring epidermal cells and into the cortical cells of growing hair. Variations in skin colour in different races and in most disorders of hyperpigmentation are related to an increased rate of formation of melanin

rather than melanocyte proliferation (Fitzpatrick and Szabo, 1959).

Lerner and Case state that pigment-cell or melanocyte opacity is regulated by many factors which may be considered as (1) factors operating at enzyme level that affect the amount of pigment within the cell, and (2) factors operating at a higher level of organization that affect the movement and distribution pattern of melanin granules within the cell. Altered enzymic activity accounts for some clinical changes in pigmentation such as those occurring in albinism, phenylpyruvic oligophrenia, and heavy-metal toxicity. Melanocyte-stimulating hormones of the pituitary gland (M.S.H.) darken the pigment cells of man and lower animals. Melatonin, recently isolated from the pineal glands of cows, lightens the pigment cells of frogs and decreases the melanin content of frog skin. Its effect in human pigmentation is not known. These darkening and lightening effects are produced by the dispersion or concentration of melanin granules within the melanocytes. A study of inhibitors of melanin formation may provide a clue to the chemotherapeutic control of malignant melanoma.

Depigmentation of human hair may result from treatment with chloroquine (Alving *et al.*, 1948). This drug evidently acts only on red, blonde, or light-brown hair; no effect has been noted in black-haired people. Skin colour is unaffected and the mechanism of depigmentation is unknown. It had no *in-vitro* effect on tyrosinase activity.

Dr. W. W. Heseltine, of the Squibb Institute for Medical Research, informed me in 1961 that there has been no published report on mephenesin which makes any reference to depigmentation of hair or skin. He recalled, however, that in therapeutic trials of the drug by Dr. Engler (1954, 1955) the question did arise in one or two female patients. Extensive inquiries and laboratory studies were undertaken by the manufacturers, but no confirmation was obtained. Subsequently, Engler made no reference to hair depigmentation in his two publications, but in a personal communication in 1962 he said that, although the odd case of depigmentation of hair may have been noted at the time in the spastic mental-defective group comprising his clinical material, he came to the conclusion that it could not have been attributed to the drug. Professor Harvey Blank (1958), of Florida, U.S.A., at the end of a discussion on the depigmentation effect of chloroquine (Saunders *et al.*, 1959), stated that a similar effect had been reported as a result of mephenesin therapy. In a personal communication he informed me that he has never actually seen this effect, but he understood from Messrs. Squibb & Sons Ltd. (manufacturers of "tolseram"), when they made their inquiries in 1954, that the possibility had been raised. Professor Blank states that this was the only source of information for his statement.

#### Summary

Mephenesin ("myanesin") carbamate can cause depigmentation of scalp hair. The effect has been observed in six patients—four female and two male. Five were suffering from multiple sclerosis and one from a post-traumatic hemiplegia. The degree of depigmentation seems to depend on the dosage of the drug and the duration of treatment. In the most striking cases

the hair turned from dark brown to blonde in three months when the patients were taking 20 tablets (10 g.) daily. There were no general ill-effects and the colour change was much appreciated by the four women patients, who seemed inclined to keep it a secret.

The manner in which mephenesin exerts this effect on melanogenesis is not known, but experimental studies are being undertaken.

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## FOETAL ERYTHROCYTES IN THE MATERNAL CIRCULATION

BY

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Since the publication by Zipursky *et al.* (1959) of a modification of the Kleihauer technique for the identification of foetal red cells, numerous workers have reported the finding of foetal erythrocytes in the maternal circulation soon after delivery. The present investigation was undertaken to find out if any factors related to pregnancy or delivery could be said to influence this occurrence.

#### Method

Specimens of venous blood were collected from 165 women who had experienced no complications in pregnancy or labour, and films were prepared by the Zipursky method. It was not found necessary to stain the films. Since it was intended to find out whether or not a transplacental leak had occurred, without reference to its magnitude or possible clinical consequences, even a single foetal cell observed in two longitudinal traverses of a microscope slide—that is, an average of 120,000 maternal red cells—was recorded as a positive.

The cases were studied with particular reference to parity, duration of labour, weight, and condition of the placenta and its method of expulsion. Since it was also thought that some degree of anoxia in the foetus, by reason of the possible effect on capillary permeability, might predispose to a leakage of foetal cells, the infants were assessed at birth by means of the Apgar (1953) score. Because foetal red cells which are ABO incompatible with those of the mother are rapidly eliminated, all specimens were collected within 24 hours of delivery.

#### Results

In the 165 cases studied foetal cells were found in 83, but in only 9 of these did the number of foetal cells observed amount to 0.02% or more of the total erythrocytes. In one case 1.5% of foetal cells was observed. No foetal cells at all were seen in the films from the remaining 82 cases. This means that in 50%

of the women there had been an escape of foetal cells into the maternal circulation. This agrees with the work of Cohen and Zuelzer (1962). That these figures are uninfluenced by parity is demonstrated in the Table.

	Foetal Cells Present	Foetal Cells Not Present
1st pregnancy .. ..	26	30
2nd " .. ..	24	22
3rd " .. ..	11	11
4th " .. ..	11	7
5th " .. or over ..	11	12

Duration of labour seemed to have no bearing on transplacental bleeding, since it was found to have occurred as commonly in women who had short labours as in those in whom labour was protracted. Further, when the first, second, and third stages were considered separately the figures remained the same.

The method of expulsion of the placenta was considered in each case and the balance between those patients who had and those who had not foetal cells remained unaffected whether the placenta was expelled spontaneously or assisted by fundal pressure. In cases where the placenta was noted as being calcified or infarcted, again there was no difference in the number of "positives" between these and the placentae which did not show these characters.

Among 105 patients with a placenta weighing less than 1½ lb. (680 g.), 43.8% had foetal cells present in the blood. The corresponding proportion among the 60 patients with placentae weighing more than 1½ lb. was 61.7% ( $\chi^2=4.184$ ;  $n=1$ ;  $P<0.05$  but  $>0.025$ ). The figures are sufficiently suggestive to point to a relationship between transplacental bleeding and the size of the placenta, and deserve further investigation. It is a result which would be expected, since in the heavier placentae a larger foeto-maternal area of contact would be available to permit transplacental bleeding.

When the ABO groups of mother and baby were noted and there was ABO compatibility, 70 cases were found with foetal cells against 62 without; but that ABO cells can be found in spite of ABO incompatibility if they are looked for carefully enough and soon enough after delivery was shown in 13 out of the 33 examined. This is a higher proportion than that reported by Fraser and Raper (1962), who found a 16% incidence, or by Cohen and Zuelzer (1962), who found 15%; but larger numbers of cases might well reduce this difference.

By the Apgar assessment the infant is given a score of from 0 to 10 for its condition of heart, respiration, tone, reflexes, and colour one minute after birth. This is repeated after five minutes, and in addition the time for the establishment of sustained respiration is noted. The results when investigated by this method showed no difference in the incidence of transplacental escape of foetal cells between the babies who were given full marks at birth and those who were given a lower assessment.

In conclusion it is suggested that transplacental bleeding of slight degree which can be demonstrated in 50% of cases within 24 hours of delivery can hardly be regarded as an abnormality, but the factors which predispose to its occurrence in otherwise normal cases remain unknown.

#### Summary

Specimens of venous blood were collected within 24 hours of delivery from 165 women in whom pregnancy